## REMARKS

This document is submitted in response to the Office Action dated July 26, 2006 ("Office Action"). As suggested by the Examiner, Applicants amended claims 5-8, 22, 23, 26, and 27 to promote clarity and corrected status identifiers of claims 28-31. Support for "isolated cell" can be found in the specification, at page 17, lines 16-31 and page 19, lines 12-18.[1] Claim 2, reciting "a [polypeptide] fragment," was amended to specify the minimum length of the fragment, support for which appears at page 13, lines 16-18 of the specification. No new matter has been introduced.

Claims 1-31 are pending. Claims 9-19 and 28-31 have been withdrawn from further consideration as drawn to non-elected inventions. Claims 1-8 and 20-27 are under examination, and claims 1, 3, 20, and 21 have been allowed. Reconsideration of claims 2, 4-8, and 22-27 is respectfully requested in view of the remarks below.

### Objection under 37 CFR 1.121

The Examiner stated that the status identifiers of claims 28-31 did not comply with 37 CFR 1.121. See the Office Action, pages 2-3, carryover paragraph. Applicants have corrected them as suggested by the Examiner and submit that new identifiers comply with 37 CFR 1.121.

### Rejection under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 5-7, 22-23, and 27 for indefiniteness, alleging that "it is unclear whether the term 'transformant' recited in these claims includes cells within an animal or the whole animal itself." See the Office Action, page 4, lines 13-14. In view of the alleged indefiniteness, he further stated that the word "harboring" recited in the claims is also unclear. See the Office Action, page 4, lines 19-20. The Examiner suggested replacing "transformant" with "isolated transformed cell" to overcome the rejection. See the Office Action, page 3,

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[1]These two passages of the specification describe various isolated cells that are transformed with nuclei acids. The phrase "isolated cell" does not have to be set forth verbatim in the specification. In *In re Wright*, 9 USPQ2d 1649 (Fed. Cir. 1989), the Federal Circuit, in reversing a Board's 35 U.S.C. § 112, first paragraph rejection, held that there was adequate written description support for applicant's claim limitation, despite the fact that it was not set forth "in *haec verba*" (i.e., "in these words" or "verbatim") in the specification.

lines 9-17. Applicants have amended the claims as suggested and request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 24-27 for lack of enablement. See the Office Action, page 5, line 6 to page 6, line 12.

Independent claim 24 is drawn to an isolated nucleic acid comprising a nucleotide sequence encoding a protein that comprises the amino acid sequence of SEQ ID NO: 2, 4, or 17 (i.e., NR10.1, NR10.2, and NR10.3, respectively), with a single amino acid replacement, deletion, insertion, or addition, wherein the protein binds to a hematopoietin factor. The Examiner first stated that "the specification does not identity any specific amino acid in any of the claimed sequences that can be deleted or replaced or identify position in the proteins where an additional amino acid can be added or inserted such that binding to a hematopoietin factor is preserved." See the Office Action, page 5, lines 14-17.

Applicants respectfully traverse. MPEP 2164.08 states, in relevant part, that

> [t]he Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art.

As indicated in the specification, it is recognized in the art that a single amino acid mutation is not likely to significantly affect protein function. See page 10, lines 7-12. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie *et al.*, "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990). A copy of this article is attached hereto as "Exhibit A." Specifically, Bowie *et al.* teaches, at page 1306, right column, second full

paragraph, that proteins in fact are tolerant of amino acid substitutions. It cites as evidence a study carried out on the *lac* repressor. Of approximately 1500 single amino acid substitutions at 142 positions in this protein, about one-half of the substitutions were found to be "phenotypically silent": that is, had no noticeable effect on the activity of the protein (page 1306, right column, lines 14-17). Presumably the other half of the substitutions exhibited effects ranging from slight to complete abolishment of repressor activity. Thus, one can expect, based on Bowie *et al.*'s teachings, to find over half (and possibly well over half) of random substitutions in a given protein to result in mutated proteins with full or nearly full activity. These are far better odds than those at issue in *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988), in which the court said that screening many hybridomas to find the few that fell within the claims was not undue experimentation.

Accordingly, base on the level of knowledge in the art, one skilled in the art would predict that even random single amino acid mutation in NR10.1, NR10.2, or NR10.3 will predictably result in a majority of the mutants' having full or partial activity. Here, the specification teaches that NR10.1, NR10.2, and NR10.3 are members of a hematopoietin-factor-binding protein family and bind to hematopoietin factors. A number of domains are conserved among members of the family and are involved in the proteins' function. See Dillon *et al.*, Diveu *et al.*, and Kermebeck *et al.*, which were discussed in the last two responses. For example, each of the three proteins NR10.1, NR10.2, and NR10.3 contains conserved cysteine residues, a YR motif, a PP-W motif, a WS motif, and a PXP motif, all hallmarks of the hemopoietin receptor family. See the specification, page 3, lines 20-27, and page 46, lines 6-24. Collectively, these structures are characteristic of the extracellular domain of hemopoietin receptor family members. One of ordinary skill in the art would understand that mutating within these conserved regions would increase the risk of altering function, and so would avoid doing so if maintaining function were the goal. Also, the specification provides guidance as to how to introduce mutations and which amino acids can be introduced. See page 9, lines 9-19 and page 9, line 29 to page 10, line 6.

Given the guidance of the specification and the level of knowledge and skill in the art, a skilled artisan has "[a]ll that is necessary … to practice the claimed invention." Specifically, he

or she would recognize that a single amino acid mutation can be introduced at a site outside the conserved motifs so that NR10.1, NR10.2, or NR10.3's binding to a hematopoietin factor is preserved.

It is also the Examiner's position that

> [i]n the absence of any known ligand for NR10, or hematopoietin factor which binds to NR10, the skilled artisan would not be able to predict whether any single amino acid replacement, deletion, insertion, or addition to any portion of the NR10 proteins, or particularly the extracellular domain of these proteins would affect the binding of the putative receptor protein to a hematopoietin factor. As such , it would require undue experimentation for the skilled artisan to identify putative ligands for the three disclosed receptor proteins and then further test which of amino acids present in the receptor proteins can be replaced or deleted, or which amino acid can be inserted or added without affecting the ability of the receptor to bind to a ligand.

See the Office Action, page 6, lines 4-10.

Applicants disagree. As discussed above, NR10.1, NR10.2, and NR10.3 proteins include hallmark domains conserved in the hemopoietin receptor family. These domains are characteristic of the extracellular domain of hemopoietin receptor family members, to which their ligands bind. Given the teaching and the level of knowledge and skill in the art, a skilled artisan would be able to predict that mutations in the conserved motifs would affect the binding activity, even in the absence of a known ligand. Thus, the Examiner's position is untenable.

For the above reasons, Applicants submit that claim 24 meets the enablement requirement. Claims 25-27 depend from claim 24. At least for the same reasons, they also satisfy the enablement requirement. It is therefore requested that the rejection be withdrawn.

Rejection under 35 U.S.C. § 102(e)

The Examiner rejected claims 2, 4, 6, and 8 as being anticipated by U.S. Patent No. 6,642,360 ("the '360 patent"). These claims cover an isolated nucleic acid comprising a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 2, 4, or 17 or a fragment thereof; a related vector; and related isolated cells. According to the Examiner, the '360 patent

"teaches SEQ ID NO:91, which has a 100% sequence identity to a fragment of SEQ ID NOs:2, 4, and 17" (emphasis added). See the Office Action, pages 7-8, carryover paragraph. The Office Action does not identify the particular fragment of SEQ ID NOs:2, 4 and 17 to which this sentence refers, and does not supply a sequence alignment, thereby making it difficult to respond to this rejection. Applicants therefore generated a sequence alignment of the '360 patent's SEQ ID NO:91 with each of SEQ ID NOs:2, 4 and 17 of the present application, and examined each of the three alignments for regions of 100% sequence identity between the aligned proteins. The three alignments are shown in Exhibit B.

The alignments show that the longest stretch of identity between the prior art sequence (SEQ ID NO:91) and any of SEQ ID NOs:2, 4 and 17 is a mere three consecutive residues, found in SEQ ID NOs:2 and 17. Applicants have amended claim 2 to specify that the fragment is at least 7 amino acid residues in length. As the '360 patent does not disclose a nucleic acid comprising a sequence encoding a fragment of any of SEQ ID NOs:2, 4 or 17 at least 7 residues in length, it does not anticipate claim 2, as amended. Neither does it anticipate claims 4, 6, and 8, all of which depend from claim 2. Applicants respectfully request that the rejection be withdrawn.

## CONCLUSION

Applicants submit that claims 2, 4-8 and 22-27, like claims 1, 3, 20, and 21, are in condition for allowance, and such action is respectfully requested.

Enclosed is a Petition for Three Months Extension of Time. The fees in the amount of $1020 are being paid concurrently on the Electronic Filing System (EFS) by way of Deposit Account authorization.

Please apply any other required fees to deposit account 06-1050, referencing the attorney docket number shown above.

Respectfully submitted,

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